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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
|---|---|---|---|---|
| 10/735,118 | 12/11/2003 | Sarah S. Bacus | CST-213 | 4570 |

7590 01/21/2010

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| EXAMINER | |
|---|---|
| GODDARD, LAURA B | |
| ART UNIT | PAPER NUMBER |
| 1642 | |

| MAIL DATE | DELIVERY MODE |
|---|---|
| 01/21/2010 | PAPER |

**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/735,118 | BACUS ET AL. | |
| | Examiner | Art Unit | |
| | LAURA B. GODDARD | 1642 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *02 October 2009*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *84-86,88-102 and 104-113* is/are pending in the application.

4a) Of the above claim(s) *86,90-98,102,104 and 108-110* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *84, 85, 88, 89, 99-101, 105-107, and 111-113* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

## DETAILED ACTION

1. The Amendment filed October 2, 2009 in response to the Office Action of April 2, 2009, is acknowledged and has been entered. Claims 84-86, 88-102, and 104-113 are pending. Claims 84 and 89 are amended. Claims 1-83, 87, and 103 are canceled. Claims 86, 90-98, 102, 104, and 108-110 remain withdrawn. Claims 84, 85, 88, 89, 99-101, 105-107, and 111-113 are currently being examined as drawn to the elected species of assaying phosphorylation of an S6 ribosomal polypeptide and expression of an IGFR.

### Rejection Maintained

### *Claim Rejections - 35 USC § 112*

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

2. **Claims 84, 85, 87-89, 99-101, 105-107, 111-113 remain rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement.** The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention (see section 8 of the previous Office Action).

The factors to be considered in determining whether undue experimentation is required are summarized In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988). The court in Wands states: "Enablement is not precluded by the necessity for some experimentation such as routine screening. However, experimentation needed to practice the invention must not be undue experimentation. The key word is 'undue,' not 'experimentation.' " (Wands, 8 USPQ2d 1404). Clearly, enablement of a claimed invention cannot be predicated on the basis of quantity of experimentation required to make or use the invention. "Whether undue experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations." (Wands, 8 USPQ2d 1404). The factors to be considered in determining whether undue experimentation is required include: (1) the quantity of experimentation necessary, (2) the amount or direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.

The claims are now drawn to a method for identifying a HER-2 over-expressing mammalian tumor that is likely to respond to a HER-2 directed therapy, the method comprising the steps of:

(i) assaying a sample obtained from the mammalian tumor to detect a pattern of:

(a) phosphorylation of an S6 ribosomal polypeptide, wherein said detected pattern of phosphorylation of S6 ribosomal polypeptide is determined using an antibody that binds to an epitope comprising a phosphorylated serine residue at position 235 in SEQ ID

NO:2;

(b) expression of an IGFR-1 (Insulin-like Growth Factor Receptor-1) polypeptide; and

(ii) comparing said pattern to a pattern detected in a sample obtained from a non- tumor tissue or cell sample, wherein a change in the detected pattern identifies said mammalian tumor as likely to respond to a HER-2 directed therapy (claim 84, 87, 89, 101, 103, 105, 112), the method of claim 84, wherein the detected pattern is increased phosphorylation of S6 ribosomal polypeptide, accompanied by decreased expression of IGFR polypeptide in the mammalian tumor as compared to said non-tumor tissue or cell sample, wherein said pattern identifies said tumor as likely to respond to a HER-2 directed therapy (claim 85), wherein said mammalian tumor is a breast tumor (claims 88, 107), the method of claim 89, wherein the detected pattern of expression and phosphorylation is determined subsequent to contacting the sample obtained from the mammalian tumor with a HER-2 directed therapy (claim 99), wherein the HER-2 directed therapy comprises rhuMAb HER-2 (claims 100, 111), wherein the mammalian tumor is identified as overexpressing HER-2 (claims 106, 113).

The specification discloses that utilizing a panel of phospho-specific antibodies to profile signal transduction pathway activation in cellular samples from a plurality of patients having a particular disease, coupled with determining correlations among activation statuses of multiple proteins in a pathway and a given outcome (e.g. disease progression, therapeutic responsiveness, survival, etc.) enables the identification of the most relevant and statistically-significant biomarkers of the given outcome (p. 7, lines 24-26 to p. 8, lines 1-5). The specification discloses examples of detecting the presence

or absence of IGFR and presence or absence of phosphorylated S6 as correlated to response to HERCEPTIN® therapy only in breast cancer patients overexpressing HER2 (Tables 1-6). The specification demonstrates that the presence or absence of S6 phosphorylation alone was not predictably correlated to a response to HERCEPTIN® therapy (p. 27, lines 28-31; Table 4). However, the specification discloses that the presence or absence of IGFR expression predicted HERCEPTIN® therapy response, wherein IGFR negative patients had higher response rates to HERCEPTIN® therapy than IGFR positive patients (Table 2). Further, the specification discloses that 67% of patients with combined IGFR negative and phosphorylated S6 positive breast cancer responded to HERCEPTIN® therapy and only 26% of patients with combined IGFR negative and phosphorylated S6 negative samples responded to HERCEPTIN® therapy (Table 5).

In related art, Lu et al (J National Cancer Institute, 2001, 93:1852-1857) teach *in vitro* Her-2 overexpressing breast cancer cell lines with inhibited or low insulin growth factor-1 receptor (IGF-IR or IGF-1R) expression are more susceptible to trastuzumab (HERCEPTIN®) than cells with IGF-IR expression (abstract). However, Köstler et al (J Cancer Research Clinical Oncology, 2006, 132:9-18) contradict this teaching for an *in vivo* study that measured IGF-1R status in HER-2 overexpressing breast tumors and determined that response to trastuzumab therapy was independent of IGF-1R expression, meaning IGF-1R did not predict therapeutic response for patients with HER-2 overexpressing breast tumors (abstract). The study done by Köstler et al teaches the

unpredictability of using IGF-1R expression alone to determine patient response to trastuzumab.

One cannot extrapolate the teaching of the specification to the enablement of the claims because the specification does not provide any examples or guidance for a method for identifying **any HER2-overexpressing mammalian tumor** that is likely to respond to **any HER-2 directed therapy** comprising determining **any changes in pattern** of S6 phosphorylation and IGFR-1 expression **between a sample obtained from the mammalian tumor and any sample obtained from any non-tumor tissue or cell sample.** Although some dependent claims may further limit some variables (in bold) of the independent claims, they do not limit all of them. The specification provides only a nexus between HER-2 overexpressing breast tumors that are IGFR-1 expression negative and positive for S6 phosphorylation at serine residue 235 in SEQ ID NO:2 and the increased likelihood of response to HERCEPTIN® therapy. The specification provides neither guidance on nor exemplification of how to predictably correlate any detected change in pattern in IGFR-1 expression and S6 phosphorylation to any response to any HER-2 directed therapy for any cancer**.** Tockman et al (Cancer Res., 1992, 52:2711s-2718s) teach considerations necessary in bringing a cancer biomarker to successful clinical application. Although the reference is drawn to biomarkers for early lung cancer detection, the basic principles taught are clearly applicable to other oncogenic disorders and the predictable correlation between biomarkers and treatment outcome. Tockman et al teaches that prior to the successful application of newly described markers, research must validate the markers against acknowledged disease

end points, establish quantitative criteria for marker presence/absence and confirm marker predictive value in prospective population trials (see abstract). Early stage markers of carcinogenesis have clear biological plausibility as markers of preclinical cancer and **if validated** can be used for population screening (p. 2713s, col 1). The reference further teaches that once selected, the sensitivity and specificity of the biomarker must be validated to a known (histology/cytology-confirmed) cancer outcome. The essential element of the validation of an early detection marker is the ability to test the marker on clinical material obtained from subjects monitored in advance of clinical cancer and *link* those marker results with subsequent histological confirmation of disease. This irrefutable link between antecedent marker and subsequent acknowledged disease is the essence of a valid intermediate end point marker (p. 2714, see Biomarker Validation against Acknowledged Disease End Points). Clearly, prior to the successful application of newly described markers, markers must be validated against acknowledged disease end points and the marker predictive value must be confirmed in prospective population trials (p. 2716s, col 2). Given the teaching of the art, without a validated nexus provided between specific changes in phosphorylation or expression patterns for S6 and IGFR-1 and the outcome of a specific treatment for a specific disease, one of skill in the art could not predictably use the claimed changes in phosphorylation or expression patterns for S6 and IGFR-1 to identify treatment outcome to any HER-2 directed therapy for any HER-2 overexpressing cancer.

One cannot extrapolate the teaching of the specification to the enablement of the claims because the specification does not provide **any comparison** of phosphorylation

or expression patterns for S6 and IGFR-1 in the HER-2 overexpressing breast tumor samples **to patterns found in any non-tumor tissue or cell sample**. The specification discloses only the detection of the *presence or absence* of IGFR-1 expression or S6 phosphorylation and indicates such as “positive” or “negative” in Tables 2-7 of the Examples. No *changes* in detected patterns of IGFR-1 expression or S6 phosphorylation as compared to any controls are measured and used to determine response to HERCEPTIN® therapy. The instant claims require a comparison between a HER-2 overexpressing tumor and non-tumor tissue or cell sample to determine *changes* in patterns of phosphorylated S6 and IGFR-1 expression in order to identify a HER-2 overexpressing tumor that is likely to respond to HER-2 directed therapy, including HERCEPTIN® therapy, however, no such comparison is ever made in the specification and no identification of a HER-2 overexpressing tumor that is likely to respond to HER-2 directed therapy is made based on *changes in patterns* of phosphorylated S6 and IGFR-1 expression, including changes of increases or decreases. Given no nexus is provided between control comparison-based changes in patterns of phosphorylated S6 and IGFR-1 expression and the identification of a HER-2 overexpressing tumor that is likely to respond to HER-2 directed therapy, one of skill in the art could not predictably identify a HER-2 overexpressing tumor that is likely to respond to HER-2 directed therapy based on the claimed changes, and a high quantity of experimentation would be required to determine exactly what changes in patterns compared to the claimed control would predictably identify a HER-2 overexpressing tumor that is likely to respond to HER-2 directed therapy.

Therefore, in view of the state of the art, the quantity of experimentation necessary, the breadth of the claims, lack of guidance in the specification, and the absence of working examples for comparisons to determine changes in patterns that predictably identify a HER-2 overexpressing tumor that is likely to respond to HER-2 directed therapy, it would require undue experimentation for one skilled in the art to practice the invention as claimed.

**Response to Arguments**

3. Applicants argue that they have overcome the rejection with the present amendments to claims 84 and 89. Applicants amended the claims to recite S6 phosphorylation is phosphorylation of SEQ ID NO:2 at serine residue 235 and clarified that IGFR is IGFR-1 (p. 11).

The arguments have been considered but are not found persuasive. Although Applicants addressed arguments drawn to the claims broadly encompassing any phosphorylation of S6 and any IGFR expression, and although Applicants amended the claims to overcome those issues, Applicants failed to address several arguments presented by Examiner with regards to the specification failing to provide any examples or guidance for a method for identifying **any HER2-overexpressing mammalian tumor** that is likely to respond to **any HER-2 directed therapy** comprising determining **any changes in pattern** of S6 phosphorylation at serine residue at position 235 in SEQ ID NO:2 and IGFR-1 expression **between a sample obtained from the mammalian tumor and any sample obtained from any non-tumor tissue or cell sample**, as

broadly encompassed by the claims. Further, the specification does not provide **any comparison** of phosphorylation or expression patterns for S6 and IGFR-1 in the HER-2 overexpressing breast tumor samples **to patterns found in any non-tumor tissue or cell sample**. The specification discloses only the detection of the *presence or absence* of IGFR-1 expression or S6 phosphorylation and indicates such as "positive" or "negative" in Tables 2-7 of the Examples. No *changes* in detected patterns of IGFR-1 expression or S6 phosphorylation as compared to any controls are measured and used to determine response to any HER-2 directed therapy or HERCEPTIN® therapy, as required by the claims. Given no nexus is provided between control comparison-based changes in patterns of phosphorylated S6 and IGFR-1 expression and the identification of a HER-2 overexpressing tumor that is likely to respond to HER-2 directed therapy, one of skill in the art could not predictably identify a HER-2 overexpressing tumor that is likely to respond to HER-2 directed therapy based on the claimed changes, and a high quantity of experimentation would be required to determine exactly what changes in patterns compared to the claimed control would predictably identify a HER-2 overexpressing tumor that is likely to respond to HER-2 directed therapy. Undue experimentation is required to practice the claimed invention for the reasons of record.

4. All other objections and rejections recited in the Office Action mailed April 2, 2009 are hereby withdrawn in view of amendments and arguments.

5. **Conclusion:** No claim is allowed.

6. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 C.F.R. ' 1.136(a).

A SHORTENED STATUTORY PERIOD FOR RESPONSE TO THIS FINAL ACTION IS SET TO EXPIRE THREE MONTHS FROM THE DATE OF THIS ACTION. IN THE EVENT A FIRST RESPONSE IS FILED WITHIN TWO MONTHS OF THE MAILING DATE OF THIS FINAL ACTION AND THE ADVISORY ACTION IS NOT MAILED UNTIL AFTER THE END OF THE THREE-MONTH SHORTENED STATUTORY PERIOD, THEN THE SHORTENED STATUTORY PERIOD WILL EXPIRE ON THE DATE THE ADVISORY ACTION IS MAILED, AND ANY EXTENSION FEE PURSUANT TO 37 C.F.R. ' 1.136(a) WILL BE CALCULATED FROM THE MAILING DATE OF THE ADVISORY ACTION. IN NO EVENT WILL THE STATUTORY PERIOD FOR RESPONSE EXPIRE LATER THAN SIX MONTHS FROM THE DATE OF THIS FINAL ACTION.

7. Any inquiry concerning this communication or earlier communications from the examiner should be directed to LAURA B. GODDARD whose telephone number is (571)272-8788. The examiner can normally be reached on 7:00am-3:30pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms can be reached on 571-272-0832. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Laura B Goddard/
Primary Examiner, Art Unit 1642